EXHIBIT

ANALYSIS OF SCHWARTZ

USPN 6,562,798; US PUBLICATION 2004/0092468; WO99/62923

Three disclosures referred to in OAs, but all the same specification.

What did Schwartz invent?

Abstract says it: Immunomodulatory oligonucleotide compositions are disclosed. These oligonucleotides comprise an immunostimulatory hexanucleotide sequence comprising a modified cytosine. These oligonucleotides can be administered in conjunction with an immunomodulatory peptide or antigen.

Actual embodiments disclosed: (Claim 1 of '798 patent) 1. An immunomodulatory polynucleotide comprising an immunostimulatory sequence (ISS) comprising 5'-purine-purine-mC-G-pyrimidine-pyrimidine-3', wherein mC is a cytosine modified at position C-5 with a halogen. Sole exemplification is wherein halogen is bromine. No actual embodiment in which G is anything but deoxyguanosine.

What is Scwartz's broadest reasonable disclosure?

Broader unexemplified disclosure: A composition of the subject invention is a modified ISS which is capable of eliciting a desired immune response upon administration. The term "modified ISS" as used herein refers to oligonucleotide sequences that effect a measurable immune response and comprise a **CG dinucleotide** in which the C residue is modified by addition to C-5 and/or C-6 of an electron-withdrawing moiety. (Emphasis added) If Schwartz intended to describe an ISS in which C is modified and G is modified, or in which only G is modified, he knew how to do it. Thus this sentence describes an ISS having a CG dinucleotide in which C is modified and G is not.

Description of synthesis is inconsistent with G of CG dinucleotide being modified: Schwarz teaches: The preparation of base-modified nucleosides, and the synthesis of modified oligonucleotides using said base-modified nucleosides as precursors, has been described, for example, in U.S. Pat. Nos. 4,910,300, 4,948,882, and 5,093,232. These base-modified nucleosides have been designed so that they can be incorporated by chemical synthesis into either terminal or internal positions of an oligonucleotide. Such base-modified nucleosides, present at either terminal or internal positions of an oligonucleotide, can serve as sites for attachment of a peptide or other antigen. (emphasis added) If the G of a CG dinucleotide is modified to serve as a site for attachment of a peptide or other antigen, the compound would be inactive.

Paragraph relied upon in OAs: The heterocyclic bases, or nucleic acid bases, which are incorporated in the modified ISS can be the naturally-occurring principal purine and pyrimidine bases, (namely uracil or thymine, cytosine, adenine and guanine, as mentioned above), as well as naturally-occurring and synthetic modifications of said principal bases. Those skilled in the art will recognize that a large number of "synthetic" non-natural nucleosides comprising various heterocyclic bases and various sugar moieties (and sugar analogs) are available in the art, and that as long as other criteria of the present invention are satisfied, the modified ISS can include one or several heterocyclic bases other than the principal five base components of naturally-occurring nucleic acids. Preferably, however, the heterocyclic base in the modified ISS includes, but is not limited to, uracil-5-yl, cytosin-5-yl, adenin-7-yl, adenin-8-yl, guanin-7-yl, guanin-8-yl, 4-aminopyrrolo [2.3-d] pyrimidin-5-yl, 2-amino-4-oxopyrolo [2,3-d] pyrimidin-5-yl, 2-amino-4-oxopyrrolo [2.3-d] pyrimidin-3-yl groups, where the purines are attached to the sugar moiety of the

modified ISS via the 9-position, the pyrimidines via the 1-position, the pyrrolopyrimidines via the 7-position and the pyrazolopyrimidines via the 1-position. (emphasis added)

> *Notes*: (1) Reference to A and U derivatives clearly indicates that ISS is referring to more than the CG dinucleotide. (2) Substitution is permitted only as long as "other criteria of the present invention are satisfied". (3) Axiomatic that in legal interpretation, the general gives way to the specific.

So what "other criteria of the invention" must be satisfied?

Must look at the broadest minimal disclosure, so ISS must (1) effect a measurable immune response (functional) and (2) comprise a **CG dinucleotide** in which the C residue is modified by addition to C-5 and/or C-6 of an electron-withdrawing moiety. A "CG dinucleotide in which the C residue is modified" is not a CG dinucleotide in which the G is modified.

Why is this the broadest reasonable interpretation of Schwartz?

(1) Schwartz describes a **CG dinucleotide** in which the C is modified, not a CG dinucleotide in which the C and/or G is modified. Could have said this, but didn't. (plain language doctrine)
(2) Schwartz discloses no actual embodiment in which the G of a CG dinucleotide is modified. (not an enabling disclosure for such an embodiment that retains immunostimulatory activity)
(3) No prior art at the time suggested that an ISS in which the G of a CG dinucleotide could be modified while retaining immunostimulatory activity. (no reasonable expectation of success)
(4) Specific must be given priority in interpretation over general. (Schwartz's laundry list of possible modified bases can't substitute for requirement for G in CG dinucleotide)
(5) No claim, not even a dependent claim, and not even in the unexamined published applications, ever attempted to claim an ISS in which the G is modified. (Schwartz did not regard such an embodiment as even part of his invention)
(6) Entire emphasis of the application is that C of a CG dinucleotide can be modified while retaining immunostimulatory activity. No efforts to demonstrate same for G.
(7) Schwartz's description of synthesis of compounds is consistent only with the substitution with modified nucleobases being at a position other than at the G of the CG dinucleotide. (doctrine of consistent interpretation of identical terms)

Conclusion

ISS of Schwartz may contain other nucleobase analogs, but not as a substitute for the G of the CG dinucleotide.